



Zwitterionic (pyrrolidine-2,2-diyl)bisphosphonic acid at 100, 150 and 293K

Gilles Olive, Diane D. Ellis, Didier Siri, François Le Moigne, Martin Lutz, Anthony L. Spek, Paul Tordo, Jean-Pierre Reboul

► To cite this version:

Gilles Olive, Diane D. Ellis, Didier Siri, François Le Moigne, Martin Lutz, et al.. Zwitterionic (pyrrolidine-2,2-diyl)bisphosphonic acid at 100, 150 and 293K. *Acta Crystallographica Section C: Crystal Structure Communications* [1968-2013], 2000, C56 (6), pp.720-722. hal-00662589

HAL Id: hal-00662589

<https://hal.science/hal-00662589>

Submitted on 24 Jan 2012

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Zwitterionic pyrrolidine-2,2-diylbis(phosphonic acid) at 100, 150 and 293 K

Gilles Olive, Dianne D. Ellis, Didier Siri, François Le Moigne, Martin Lutz, Anthony L. Spek, Paul Tordo and Jean-Pierre Reboul

Copyright © International Union of Crystallography

Author(s) of this paper may load this reprint on their own web site provided that this cover page is retained. Republication of this article or its storage in electronic databases or the like is not permitted without prior permission in writing from the IUCr.

Zwitterionic pyrrolidine-2,2-diylbis-(phosphonic acid) at 100, 150 and 293 K

Gilles Olive,^a Dianne D. Ellis,^{b*} Didier Siri,^a François Le Moigne,^a Martin Lutz,^b Anthony L. Spek,^b Paul Tordo^a and Jean-Pierre Reboul^c

^aUMR 6517-CNRS Université d'Aix-Marseille I et III, Av. Esc. Normandie Niemen, Case 521, 13397 Marseille CEDEX 20, France, ^bLaboratory of Crystal and Structural Chemistry, Bijvoet Center for Biomolecular Research, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands, and ^cGroupe d'Enseignement et de Recherche en Chimie Thérapeutique, Organique et Physique, Faculté de Pharmacie, 27 boulevard Jean-Moulin, 13385 Marseille CEDEX 5, France

Correspondence e-mail: d.d.ellis@chem.uu.nl

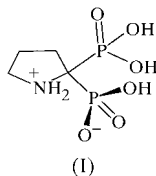
Received 18 February 2000

Accepted 10 March 2000

The title compound, C₄H₁₁NO₆P₂, reveals a two-dimensional network of P—O—H...O=P and N—H...O=P hydrogen-bond interactions, forming molecular slabs parallel with the (010) plane. One O—H...O interaction is distinct within these sets: whilst forming the shortest intermolecular hydrogen bond, it possesses a short P—O(H) bond of 1.5291 (10) Å. Weak C—H...O contacts link individual stacks to produce a three-dimensional array. The compound is zwitterionic: one H atom from a P—O—H group has transferred to the pyrrolidine ring N atom.

Comment

The non-protonated forms of *gem*-bisphosphonic acids produce chelating compounds with alkaline earth cations using their O and N atoms. The ability of pyrrolidin-2,2-diylbis(phosphonic acid), (I), to chelate with Ca has several applications, for example in the manufacture of toothpastes and mouthwashes (Plöger *et al.*, 1976; Nelson & Smitherman, 1992; Nugent *et al.*, 1993). Other related complexes have shown biological activity in agents such as antivirals and herbicides, and are components in medicines for bone diseases (Niemi *et al.*, 1999). We present here the crystal structure of (I).



The same crystal was measured at three temperatures (293, 150 and 100 K) to see if any differences could be observed in the crystallographic environment. These included whether the

crystal structure remained the same upon cooling, apart from the ubiquitous effects of lattice contraction, whether there was a reduction in thermal vibrations, or if a low temperature solid–solid transition had occurred. Initial analysis revealed only minor structural differences at each temperature. Therefore, the following discussion applies to all structure analyses, irrespective of the experimental temperature. The numerical parameters presented in Tables 1 and 2 concern the 100 K dataset, whilst those for 150 and 293 K are available in the CIF. Fig. 1 shows compound (I); the adopted numbering scheme was the same in each analysis.

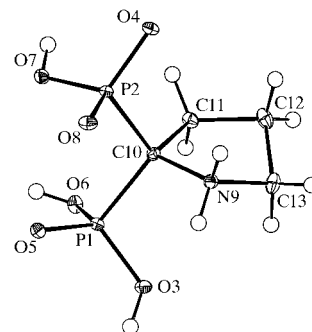


Figure 1

PLATON representation (Spek, 1999) of (I) with displacement ellipsoids at the 50% probability level. H atoms are drawn as spheres of arbitrary radii.

Compound (I) possesses a zwitterionic structure (Harris, Jackson *et al.*, 1988; Harris *et al.*, 1989), with one H atom from a phosphonate group transferring to the pyrrolidine ring N atom. The protonation at the N atom leads to an increase in the C—N bond distances and the expected tetrahedral angles at the N atom: C13—N9—C10 = 107.20 (10)°. Both P atoms exhibit distorted tetrahedral geometries: the bond angles around P1 and P2 range from 104.54 (6) to 115.34 (6)° and 103.81 (6) to 113.18 (6)°, respectively. The P centres are fairly close, due to their bisecting positions relative to C10 on the pyrrolidine ring: P1—C10—P2 = 110.54 (7)°. The intramolecular P...P distance of 3.035 (3) Å correlates with the coupling constant obtained from ³¹P solid-state NMR experiments (Magusin *et al.*, 2000). Two distinctive peaks (from the inequivalent P atoms) were found in both the room- and low-temperature ³¹P solid-state NMR spectra.

In phosphonates, the P—O bond length order is P=O < P—O[−] < P—O(H). Thus, by inspection of these distances, the nature of the bond (and for example the presence or absence of an H atom) can be assigned. Clearly, the P—O6(H) and P—O7(H) bond lengths in (I) are much longer than the other four P—O bond distances, and indeed H atoms were located on these O atoms in the difference Fourier electron-density maps. An H atom was also located on O3, but the P—O3(H) bond of 1.5291 (10) Å is significantly shorter than P—O6 or P—O7. A search of the Cambridge Structural Database (Allen & Kennard, 1993) revealed several other phosphonate/phosphonic acid species with a P—O(H) bond in this range. Other groups (Polyanchuk *et al.*, 1985; Clegg *et al.*, 1992) have also commented on the variance of P—O(H) bond lengths in phosphonate and phosphonic acid compounds.

Due to small differences between the P=O and P—O[−] bond distances in (I), their assignment is more complex; P=O5 has double bond characteristics, but for atoms O4 and O8 on P2, an initial assessment was inconclusive. Additional evidence should, in some cases, be acquired from the bond angles: the charge and lone-pair repulsions of the P—O[−] atoms should produce wider angles than the corresponding P=O groups. Unfortunately, the O=P—O and O—P—O[−] valence angles are of a similar magnitude, indicating that the negative charge is spread over the O4—P2—O8 group, and so a clear distinction could not be made. Only by inspection of the hydrogen-bonding interactions, made by atoms O4 and O8, did the circumstances become clearer.

All acidic H atoms (on O and N atoms) participate in a two-dimensional array of P—O—H...O=P and N—H...O=P hydrogen bonds (Table 2; part of the network is illustrated in Fig. 2). The O8 atom is a single hydrogen-bond acceptor, whilst O4 and O5 are double acceptors. The P—O—H groups (O3, O6 and O7), together with N9, can be considered as the hydrogen-bond donors.

The phosphonate groups P1—O6 and P2—O7 form hydrogen-bonded cyclic dimers around crystallographic inversion centres located at (0,0,1) and (0,0, $\frac{1}{2}$), respectively. These form first-level graph sets of the type $R_2^2(8)$ (Etter *et al.*, 1990; Bernstein *et al.*, 1995) to O5 and O4, respectively. The acidic H atoms on the N atoms, H9A and H9B, both form $R_2^2(10)$ rings, the former with O4 across special position ($\frac{1}{2},0,1$) and the latter with O5, located at ($\frac{1}{2},0,\frac{1}{2}$).

The P—O3 bond length is severely contracted, being 1.5291 (10) Å, but this bond participates in the shortest hydrogen-bond interaction, with O8, with graph-set descriptor $R_2^2(12)$. The electronic nature of this interaction can be described by the negative-charge assisted hydrogen bond (Gilli *et al.*, 1994), since the O3...O8 distance is only 0.01 Å outside the range given for inorganic salts. Since P=O4 forms

two hydrogen-bond networks, whereas P—O8[−] has a single strong hydrogen-bond interaction, the assignment of P=O4 and P—O8[−] seems reasonable and the differences in bond lengths can be attributed to their intermolecular hydrogen-bonding capabilities.

The two-dimensional network of P—O—H...O=P and N—H...O=P hydrogen-bond interactions results in molecular slabs located along the *a* and *c* axes. The carbon backbone of the pyrrolidine ring protrudes into the centre of the unit cell, forcing close contacts with adjacent molecules. The network is therefore extended along the *b* axis utilizing weaker C—H...O contacts (Table 2).

The five-membered pyrrolidine ring exhibits a twist conformation, with atoms C12 and C13 displaced at distances of 0.251 (2) and −0.261 (2) Å, respectively, above and below the plane. This is consistent with the ring-puckering analysis (Evans & Boeyens, 1989; Spek, 1999), which produces parameters of $Q = 0.426$ (2) Å and $\varphi = 309.4^\circ$. The present work also complements previous studies relating the ring conformation with the hybridization of the N atom. It has been demonstrated using electron spin resonance studies (Rockenbauer *et al.*, 1997) that when the N atom has an sp^2 hybridization, as in the case of 2,2-bis(diethoxyphosphoryl)pyrrolidinoyl, the five-membered ring adopts a 3T_4 twist conformation distorted towards the E_4 form. If two methyl groups are added at C13 (position 5), as for example in 2,2-bis(diethoxyphosphoryl)-5,5-dimethylpyrrolidinoyl, the 3T_4 conformation is also found but in this case it is folded towards the E_3 envelope. In compound (I), a 4T_5 ring conformation is obtained, consistent with sp^3 hybridization at the ammonium N atom. The geometric parameters obtained from this analysis can be used for force-field parameterization of aminobisphosphonates and will be used in determining structure–activity relationships (Siri *et al.*, 2000).

Several experiments were performed to assess the effects of cooling the crystal. The variation of the unit-cell parameters (*a*, *b*, *c*, α , β , γ and *V*), P—O bond distances and O—P—O bond angles with temperature were analysed and revealed the expected trend, [for the P—O parameters, values from the rigid-body motion analysis, thermal libration studies (TLS) model, were used; Schomaker & Trueblood, 1998]. The largest observable changes occurred between the measurements at 100 and those at 150 K. The hydrogen-bond distances were also analysed with temperature, and again no noteworthy effects were seen, although three interactions lengthened on decreasing the temperature, indicating a general weakening of their hydrogen-bond strength.

The effect of temperature on the rotation of the PO₃ groups was also investigated with a TLS analysis using the program THMA11 (Schomaker & Trueblood, 1998). The phosphonate groups were defined as independent rigid bodies and the mean amplitude around their individual axes was calculated. The P2 group librates more than the P1 group (the mean amplitudes about their axes being 4.0 and 2.9 $^\circ$ ², respectively), although the numerical values for the latter were small. The preceding analyses showed that the structure remained essentially the same, with no low-temperature structural changes evident.

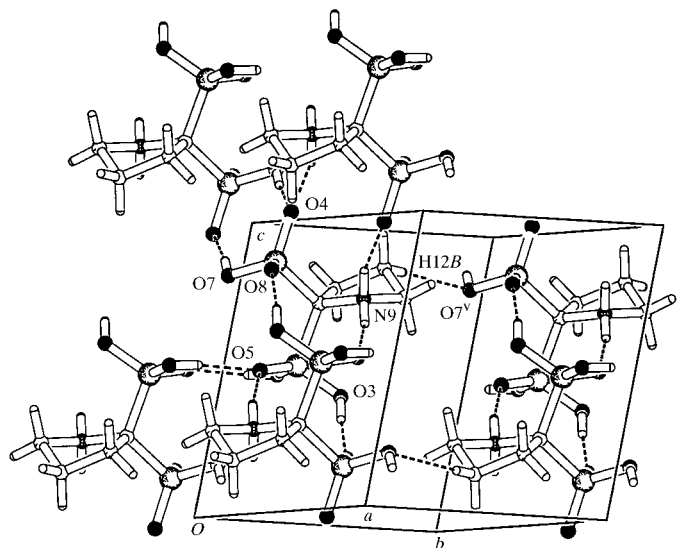


Figure 2
PLATON (Spek, 1999) plot of the hydrogen-bond network in (I). For symmetry code, see Table 2.

Experimental

The synthesis of compound (I) was carried out using the method of Zilch *et al.* (1992), which is a modification of the method of Plöger *et al.* (1976) and Nelson & Smitherman (1992). Zilch *et al.* give the synthesis of eight- to 17-membered rings, which was carried out using phosphorus oxychloride as a reagent. The synthetic route has recently been described by Olive *et al.* (1998). Colourless crystals of (I) were obtained by recrystallization from solution in pure water.

Compound (I) at 100 K

Crystal data

$C_4H_{11}NO_6P_2$	$D_x = 1.845 \text{ Mg m}^{-3}$
$M_r = 231.08$	$D_m = 1.85 (2) \text{ Mg m}^{-3}$
Triclinic, $P\bar{1}$	D_m measured by flotation
$a = 6.7397 (2) \text{ \AA}$	Mo $K\alpha$ radiation
$b = 7.7777 (3) \text{ \AA}$	Cell parameters from all reflections
$c = 8.5184 (3) \text{ \AA}$	$\theta = 2.4\text{--}27.99^\circ$
$\alpha = 78.5397 (14)^\circ$	$\mu = 0.523 \text{ mm}^{-1}$
$\beta = 85.6376 (19)^\circ$	$T = 100 (2) \text{ K}$
$\gamma = 71.8947 (18)^\circ$	Plate, colourless
$V = 415.91 (2) \text{ \AA}^3$	$0.44 \times 0.19 \times 0.12 \text{ mm}$
$Z = 2$	

Data collection

Nonius KappaCCD area-detector diffractometer	$R_{\text{int}} = 0.033$
φ scans with κ at 0° and ω scans	$\theta_{\text{max}} = 27.99^\circ$
9553 measured reflections	$h = -8 \rightarrow 8$
2003 independent reflections	$k = -10 \rightarrow 10$
1897 reflections with $I > 2\sigma(I)$	$l = -11 \rightarrow 11$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0216P)^2 + 0.3871P]$
$R[F^2 > 2\sigma(F^2)] = 0.024$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.064$	$(\Delta/\sigma)_{\text{max}} = 0.001$
$S = 1.065$	$\Delta\rho_{\text{max}} = 0.48 \text{ e \AA}^{-3}$
2003 reflections	$\Delta\rho_{\text{min}} = -0.40 \text{ e \AA}^{-3}$
162 parameters	
All H-atom parameters refined	

Table 1

Selected geometric parameters (\AA , $^\circ$) for (I).

P1—O5	1.5018 (10)	P2—O7	1.5602 (10)
P1—O3	1.5291 (10)	N9—C13	1.5058 (17)
P1—O6	1.5563 (10)	N9—C10	1.5236 (16)
P2—O8	1.5036 (10)	C12—C13	1.520 (2)
P2—O4	1.5150 (10)		
O5—P1—O3	115.34 (6)	O8—P2—O7	111.01 (6)
O5—P1—O6	112.31 (6)	O4—P2—O7	111.48 (5)
O3—P1—O6	108.44 (6)	O8—P2—C10	109.62 (6)
O5—P1—C10	110.50 (6)	O4—P2—C10	107.24 (6)
O3—P1—C10	104.92 (6)	O7—P2—C10	103.81 (6)
O6—P1—C10	104.54 (6)	C13—N9—C10	107.20 (10)
O8—P2—O4	113.18 (6)	P2—C10—P1	110.54 (7)
C13—N9—C10—C11	−16.74 (13)	C10—N9—C13—C12	37.99 (13)
N9—C10—C11—C12	−10.85 (13)	C11—C12—C13—N9	−43.88 (13)
C10—C11—C12—C13	33.98 (13)		

All H atoms were located in the difference Fourier map with their coordinates and isotropic displacement parameters freely refined. C—H distances ranged between 0.94 (2) and 0.98 (2) \AA .

Table 2

Hydrogen-bonding geometry (\AA , $^\circ$) for (I).

$D\cdots H\cdots A$	$D\cdots H$	$H\cdots A$	$D\cdots A$	$D\cdots H\cdots A$
O3—H3 \cdots O8 ⁱ	0.93 (3)	1.51 (3)	2.4427 (13)	173 (3)
O6—H6 \cdots O5 ⁱⁱ	0.81 (3)	1.77 (3)	2.5737 (14)	172 (3)
O7—H7 \cdots O4 ⁱⁱⁱ	0.84 (3)	1.70 (3)	2.5401 (14)	174 (3)
N9—H9A \cdots O4 ^{iv}	0.91 (2)	1.87 (2)	2.7501 (15)	161.6 (17)
N9—H9B \cdots O5 ⁱ	0.93 (2)	1.84 (2)	2.7392 (15)	161.4 (19)
C12—H12B \cdots O7 ^v	0.94 (2)	2.56 (2)	3.4666 (18)	163.3 (18)

Symmetry codes: (i) $1-x, -y, 1-z$; (ii) $-x, -y, 1-z$; (iii) $-x, -y, 2-z$; (iv) $1-x, -y, 2-z$; (v) $x, 1+y, z$.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *DENZO* (Otwinowski & Minor, 1997); data reduction: *DENZO*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 1999); software used to prepare material for publication: *SHELXL97*.

The authors wish to thank Julien Thibault for initial translation. The investigations were supported by the Netherlands Foundation for Chemical Research (SON) with financial aid from the Netherlands Organization of Scientific Research (NWO).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1586). Services for accessing these data are described at the back of the journal.

References

- Allen, F. H. & Kennard, O. (1993). *Chem. Des. Autom. News*, **8**, 31–37.
- Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
- Clegg, W., Iverson, P. B. & Lockhart, J. C. (1992). *J. Chem. Soc. Dalton Trans.* pp. 3291–3298.
- Etter, M. C., MacDonald, J. C. & Bernstein, J. (1990). *Acta Cryst.* **B46**, 256–262.
- Evans, G. G. & Boeyens, J. C. A. (1989). *Acta Cryst.* **B45**, 581–590.
- Gilli, P., Bertolasi, V., Ferretti, V. & Gilli, G. (1994). *J. Am. Chem. Soc.* **116**, 909–915.
- Harris, R. K., Jackson, P., Merwin, L. H., Say, B. J. & Hägele, G. (1988). *J. Chem. Soc. Faraday Trans. 1*, **84**, 3649–3672.
- Harris, R. K., Merwin, L. H. & Hägele, G. (1989). *Magn. Reson. Chem.* **27**, 470–475.
- Magusin, P. C. M. M., Olive, G. & van Oers, E. (2000). Unpublished data.
- Nelson, D. & Smitherman, H. (1992). World Patent WO 92/00721.
- Niemi, R., Vepsäläinen, J., Taipale, H. & Järvinen, T. (1999). *J. Med. Chem.* **42**, 5053–5058.
- Nonius (1998). *COLLECT*. Nonius BV, Delft, The Netherlands.
- Nugent, R. A., Murphy, M., Schlachter, S. T., Dunn, C. J., Smith, R. J., Staite, N. D., Galinet, L. A., Shields, S. K., Aspar, D. G., Richard, K. A. & Rohloff, N. A. (1993). *J. Med. Chem.* **36**, 134–139.
- Olive, G., Le Moigne, F., Mercier, A., Rockenbauer, A. & Tordo, P. (1998). *J. Org. Chem.* **63**, 9095–9099.
- Otwinowski, Z. & Minor, W. (1997). *Methods Enzymol.* **276**, 307–326.
- Plöger, W., Schmidt-Dunker, M. & Gloxhuber, C. (1976). Patent Number DE23/43147.
- Polyanchuk, G. V., Shkol'nikova, L. M., Rudomino, M. V., Dyatlova, N. M. & Makarevich, S. S. (1985). *Zh. Strukt. Khim.* **26**, 109–118.
- Rockenbauer, A., Mercier, A., Le Moigne, F., Olive, G. & Tordo, P. (1997). *J. Phys. Chem. A*, **101**, 7965–7970.
- Schomaker, V. & Trueblood, K. N. (1998). *Acta Cryst.* **B54**, 507–514.
- Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
- Siri, D., Olive, G. & Reboul, J.-P. (2000). Unpublished data.
- Spek, A. L. (1999). *PLATON*. University of Utrecht, The Netherlands.
- Zilch, H., Esswein, A. & Bauss, F. (1992). German Patent DE 41/14586A1.